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Nocturia in Male Patients with Obstructive Sleep Apnea: Efficacy of Medication for Benign Prostatic Hypertrophy

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Abstract：***Background and objectives:*** Nocturia, which is one of the symptoms in patients with benign prostatic hypertrophy（BPH), is also a well-known symptom in patients with obstructive sleep apnea（OSA). The prevalence of nocturia in OSA patients following nasal continuous positive airway pressure（nCPAP) treatment has not been investigated thoroughly, neither has the prevalence of BPH in OSA patients who need nCPAP treatment. Thus, the objective of this study was to investigate the overall prevalence of BPH that required treatment and the contribution of BPH or OSA to nocturia in OSA patients who needed nCPAP treatment.

Methods: Among 50 consecutive male patients with moderate to severe OSA over the age of 50 years who were treated by nCPAP treatment, 22 had been already examined by urologists. Therefore, 28 males with moderate to severe OSA were prospectively studied.

Results: NCPAP significantly decreased the number of nocturnal voids（2.4 ± 1.6 to 1.3 ± 1.0, p=0.0002) in 28 patients. In 18 of 28 patients requiring medication for BPH even after nCPAP treatment, the treatment further significantly decreased the number of nocturnal voids（1.5 ± 1.0 to 0.9 ± 0.8, p=0.026). Of the 22 patients seen by urologists before nCPAP, 12 had BPH requiring treatment. Thus, 30 of 50 patients（60%) had BPH requiring treatment.

Conclusions: BPH is prevalent in patients with moderate to severe OSA. Additional medication for BPH might be considered for the treatment of nocturia in them, when nCPAP is insufficient in treating their nocturia.

Key words：**Obstructive sleep apnea, Benign prostatic hypertrophy, Nocturia, Nasal continuous positive airway pressure**

Introduction

Obstructive sleep apnea（OSA) is characterized by repeated episodes of apnea during sleep. There is a growing body of evidence to support the belief that severe OSA is a risk factor for cardiovascular disease and death,[1)] not only in clinical cases[2),3)] but also in the general population.[4),5)] In addition to being one of the risk factors for cardiovascular disease, OSA induces several symptoms such as daytime sleepiness, insomnia, general fatigue, etc. Nocturia, which is one of the symptoms in

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patients with benign prostatic hypertrophy (BPH), is also a well-known symptom in patients with OSA.[6] It is believed that nocturia due to OSA may be relieved by nasal continuous positive airway pressure (nCPAP), the first-line treatment for OSA. However, the prevalence of nocturia in OSA patients following nCPAP treatment has not been investigated, thoroughly neither has the prevalence of BPH in OSA patients who need nCPAP treatment. It has been reported that nocturia produces insomnia, disturbs quality of life, and also affects mortality.[7] Therefore, it was important to investigate the overall prevalence of BPH which required treatment and the contribution of BPH or OSA to nocturia in moderate to severe OSA patients who needed nCPAP treatment.

A previous study indicated that OSA contributes substantially to causing nocturia in some individuals under the age of 50.[8] The effect on nocturia of adding treatment for BPH to nCPAP in patients over the age of 50, with moderate to severe OSA, was not clear. The current study hypothesized that both OSA and prostate diseases are associated with nocturia in those patients with OSA. To test the hypothesis, consecutive patients with OSA who were treated with nCPAP treatment were prospectively investigated.

Subjects And Methods

1 Subjects

Subjects were recruited from 55 consecutive men over the age of 50 with OSA who were admitted from August 2003 to July 2006 to the Department of Respiratory Medicine, Fukuoka University Hospital. These patients had an apnea-hypopnea index (AHI) of 20 or higher and received nCPAP. Excluded from the original 55 patients were as follow: 2 patients with brain natriuretic peptide (BNP)≥100 pg/ml before nCPAP and uncontrollable congestive heart failure; 2 patients who stopped nCPAP due to discomfort; 1 patient who used nCPAP less than 4 hours a day according to a memory card recorder. Thus, 50 patients were investigated. From these, 22 who had been previously seen by any urologists were excluded (Assessment 1, below). Therefore, the study population comprised 28 patients. This study was approved by the Ethics Committee of Fukuoka University. Informed consent was obtained from all participants.

2 Study protocol

Firstly, after carefully taking patients' past history and reviewing their clinical records, patients who had previously seen by urologists were excluded from further analysis (Assessment 1). Next, the eligible patients assessed the number of nocturnal voids at the first physical examination before introduction of nCPAP treatment (Assessment 2). Then, at 1 year after the start of nCPAP treatment, patients examined the number of nocturnal voids again and were seen by urologists regardless of whether they had nocturia or not, and also assessed their symptom using the International Prostate Symptom Score (IPSS)[9] (Assessment 3). When patients had to be seen by urologists for their nocturia at least two months after the start of nCPAP treatment due to intolerable voids, the number of nocturnal voids at this examination was used. Then, even if they were prescribed with BPH treatment or not by urologists in either case, the number of nocturnal voids using the IPSS was assessed one year after (Assessment 4).

3 OSA and PSG

All patients underwent PSG. The PSG system used was the Alice 4 (Respironics, Murrysville, PA, USA). Electroencephalogram (EEG; C3/A2, C4/A1, O1/A2), electrooculograms, chin electromyogram (EMG), tibialis anterior EMG, electrocardiogram (ECG), and chest and abdominal movements were recorded; at the same time, sensors were used to determine body position, air flow (thermistor), and oxygen saturation by pulse oximetry (SpO_2). The start of sleep and final wake-up times were determined by PSG. Waking EEG and sleep stages were determined by the criteria of Rechtschaffen & Kales.[10] Total sleep time was determined based on the EEG. Apnea was defined as a complete cessation of airflow at the nose and mouth that lasted for ≥10s. Hypopnea was defined as a ≥50% reduction in oronasal airflow for ≥10s, associated with a ≥3% fall in arterial oxygen saturation or an arousal.[11] AHI was the number of episodes of obstructive apnea, mixed apnea, and hypopnea per hour of sleep. The frequency of arousal due to apnea or hypopnea served as the arousal index. The lowest SpO_2 and the percentage of total sleep time of $SpO_2 < 90\%$ (%TST of $SpO_2 < 90\%$) were also calculated. Patients with an AHI greater than 20 underwent nCPAP treatment under the health insurance system in the Japanese government. Severity of OSA was defined by AHI as follows: no OSA (AHI<5/h), mild OSA (AHI=5-14.9/h), moderate OSA (AHI=15-29.9/h) and severe OSA (AHI≥30/h). In addition, nCPAP (REM Star: Respironics, Murrysville, PA, USA) titration was carried

out during the PSG.

4 Severity of BPH

The severity of BPH was diagnosed according to the guidelines of the Japanese Urological Association.[12),13)] The IPSS is an 8-question（7 symptom questions + 1 quality of life question）written screening tool for the symptoms of BPH.[9)] The number of nocturnal voids is included as one of their questions（"Over the past month, how many times did you typically get up to urinate from the time you went to bed at night until the time you got up in the morning?"）. The severity of each factor was classified as mild, moderate, or severe by areas of assessment, i.e. symptoms, urinary function（maximum urinary flow rate and residual urine）, and morphology（prostate volume）.[12),13),14)] In addition, overall severity（mild, moderate and severe）was determined depending on the number of items to determine that severity.

5 Assessment of sleepiness

The modified Japanese version of the Epworth Sleepiness Scale（ESS）[15)] was used to assess subjective sleepiness.

6 Statistical analysis

Data are presented as mean ± standard deviation. The effects of nCPAP titration on various sleep parameters were determined with a paired-t test. The statistical significance of differences in nocturnal voiding between Assessment 2 and Assessment 3, and between Assessment 3 and Assessment 4 was determined with Wilcoxon signed-rank test. $P<0.05$ was considered significant.

Results

1 Clinical characteristics

Twenty-eight patients completed the protocol, and their characteristics are shown in Table 1. Their age was 65.5 ± 8.9 years old and their body mass index（BMI）was 25.5 ± 3.3kg/m^2. Six patients were current smokers, 19 were ex-smokers and the remaining 3 patients were never smokers. Eighteen（64%）had hypertension（systolic blood pressure（BP）≥140mmHg and/or diastolic BP ≥90mmHg）and/or were being prescribed anti-hypertension drugs（no α blockers）. Sixteen（57%）had total cholesterol concentration ≥220mg/dl and/or triglycerides ≥150mg/dl and/or high-density lipoprotein cholesterol <40mg/dl and/or were being prescribed a statin. Eight（29%）had type 2 diabetes, but none was receiving treatment for this condition, there were no complications, and HbA1c was controlled to under 6.5% in addition to no glucose in the fasting urine.

On the ESS, they had a score of 10.9 ± 5.6, indicating that mild daytime sleepiness was noted（Table 1）. They had an AHI of 40.1 ± 14.9; 7 patients had moderate OSA and 21 had severe OSA. As a result of nCPAP titration, AHI improved significantly to 4.8 ± 5.0（$p<0.0001$）. Significant improvement was also noted in the arousal

Table 1. Characteristics of the 28 subjects

	Before nCPAP	During nCPAP titration	p value
Age, y	65.5 ± 8.9		
BMI, kg/m^2	25.5 ± 3.3		
ESS	10.9 ± 5.6		
AHI	40.1 ± 14.9	4.8 ± 5.0	<0.0001
Arousal index	37.4 ± 13.9	16.7 ± 8.6	<0.0001
REM stage, %	16.2 ± 7.7	17.6 ± 3.7	0.52
stage Ⅰ, %	42.0 ± 18.5	30.1 ± 17.5	0.054
stage Ⅱ, %	40.8 ± 15.9	49.8 ± 16.7	0.11
stage Ⅲ, %	0.7 ± 1.4	2.1 ± 3.1	0.025
stage Ⅳ, %	0.0 ± 0.0	0.0 ± 0.1	0.33
Lowest SpO_2, %	79.7 ± 7.1	90.2 ± 4.4	0.00019
%TST of SpO_2 < 90%, %	11.4 ± 15.1	2.3 ± 5.7	0.023
Snore index, %	23.9 ± 21.2	3.3 ± 8.4	0.00056

BMI: body mass index, ESS: Epworth Sleepiness Scale, AHI: apnea hypopnea index,
REM: rapid eye movement, SpO_2: oxygen saturation by pulse oximetry, TST: total sleep time

index, stage III sleep, lowest SpO_2, %TST of SpO_2 < 90% and snore index.

2 Severity of BPH and medication

Moderate to severe BPH was noted in 21 of 28 patients (75%) (mild in 7, moderate in 18, and severe in 3) at Assessment 3. The average prostate volume was 29.7 ± 16.2 ml. Eighteen patients received medication for BPH and 10 did not. Their medication was as follows: α1-blocker alone, 12 patients; phytotherapeutic agent alone, 3 patients; and their combination, 3 patients.

3 Effects of nCPAP on the changes in the number of nocturnal voids

For the 28 patients studied, the number of nocturnal voids decreased significantly with nCPAP from 2.4 ± 1.6 (Assessment 2) to 1.3 ± 1.0 (Assessment 3) (p=0.0002) (Figure 1.). The average duration of nCPAP treatment before visiting urologists was 10 months. Eighteen of the 28 patients required medication from urologists (Assessment 3). The other 10 patients did not take medications for BPH following the examinations of the urologists. Before the medication, the number of nocturnal voids in 18 patients decreased significantly as a result of nCPAP treatment, from 2.6 ± 1.7 (Assessment 2) to 1.5 ± 1.0 (Assessment 3) (p=0.0029). For the 10 patients who were not treated for BPH after they were seen by urologists, the number of nocturnal voids also decreased significantly after nCPAP treatment, from 1.9 ± 1.3 (Assessment 2) to 0.8 ± 0.8 (Assessment 3) (p=0.031) (Figure 1.).

4 Effects of medication for BPH

Following 1 year of the medications for BPH, the number of nocturnal voids in 18 patients further decreased from 1.5 ± 1.0 (Assessment 3) to 0.9 ± 0.8 (Assessment 4) (p=0.026) (Figure 1.). However, for the 10 patients who were not treated for BPH after they were seen by urologists, the number of nocturnal voids did not change significantly (0.8 ± 0.8 (Assessment 3) to 0.5 ± 0.8 (Assessment 4), p=0.083) following the next 1year of nCPAP treatment (Figure 1.).

5 Correlation between the number of nocturnal voids and physiological findings

The number of nocturnal voids prior to medication (Assessment 2) was not significantly correlated with age, PSG findings (AHI, arousal index, lowest SpO_2, %TST of SpO_2 < 90% and snore index) and prostate volume.

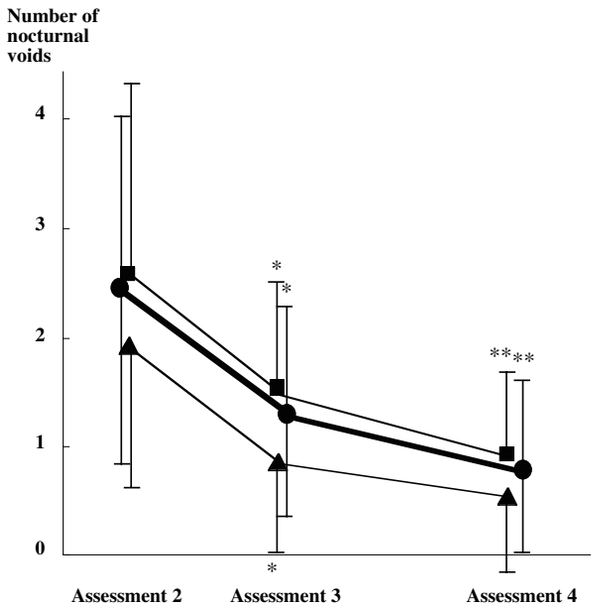

Figure 1. Changes in the number of nocturnal voids before nCPAP (Assessment 2), after nCPAP (approximately 10 months) (Assessment 3), and after checked by the urologists (approximately 12 months) (Assessment 4) in all 28 patients (●), 18 patients with BPH requiring its treatment (■), and 10 patients without BPH medication (▲). *p<0.05, versus Assessment 2; **p<0.05, versus Assessment 3.

6 Twenty-two patients who had already seen by urologists

Sixteen of the 22 patients who were excluded at Assessment 1 were diagnosed as BPH. Twelve of these 16 patients with BPH required treatment; 3 with surgery, 9 with medication, 2 with prostate cancer, 2 with ureteral calculi, 1 with prostatitis, and 1 with neurogenic bladder.

Of the 28 patients that completed the protocol, 18 had BPH requiring medication (Assessment 3). Thus, after all, among 50 patients who had entered the study, 30 patients (60%) had BPH requiring treatment.

Discussion

The current study examined male patients with moderate to severe OSA. We found out that (1) nocturia was frequently noted and the number of nocturnal voids decreased after nCPAP treatment within one year, (2) nocturia did not fully improve despite nCPAP treatment for approximately 10 months, and more than half of the

patients required additional medication for BPH, and (3) nocturia was managed better by nCPAP treatment and medication for BPH in these patients.

After middle age, nocturia is noted in many patients;[16] it diminishes their quality of life and is related to a reduced life expectancy.[7] Many patients with OSA have nocturia. Moriyama et al.[8] interviewed 73 men under the age of 50 with OSA about their nocturia, and noted that 41.1% had 2 or more voids after the start of asleep. This indicates that OSA may be a major cause of nocturia in men under the age of 50. Hajduk et al.[17] interviewed 138 patients with OSA and reported a frequency of nocturia of 47.8%; they also reported finding that AHI was positively correlated with nocturia, independent of BMI. Additionally, nocturia is reported to improve after nCPAP treatment for one night.[18),19] However, none of the previous studies has shown the effects of long-term nCPAP treatment on the number of nocturnal voids. In the present study, after 10-month nCPAP treatment, the number of nocturnal voids significantly decreased from 2.4 ± 1.6 (Assessment 2) to 1.3 ± 1.0 (Assessment 3). Two mechanisms have been proposed for nocturia in patients with OSA[20]: (1) diuresis increases as a result of an increase in atrial natriuretic peptide during sleep[21]; and (2) rapid changes in abdominal pressure during an episode of apnea directly affect bladder function, although atrial natriuretic peptide during sleep was not measured in this study.

We found that nCPAP did not eliminate nocturnal voids completely in some patients with OSA. The results in this study showed that nocturia in OSA males over 50 might be the result of BPH as well as factors related to OSA. In men, the frequency of BPH increases after middle age and lower urinary tract symptoms such as dysuria and frequent urination become manifest.[22] No previous reports have examined the degrees of contribution of OSA and BPH to nocturia. Then, current study prospectively studied the effects of nCPAP and medication for BPH on nocturia in men with OSA.

When patients were seen by urologists after long-term nCPAP treatment, medication for BPH was added for 18 of 28 patients (64%) based on Japanese guidelines for BPH. The core of the treatment is to reduce urethral obstruction due to an enlarged adenoma (mechanical obstruction) or ease constriction of the urethra (dynamic or functional obstruction) by α1-receptors in the sympathetic nervous system. In this study, additional medications for BPH significantly decreased the number of nocturnal voids from 1.5 ± 1.0 (Assessment 3) to 0.9 ± 0.8 times (Assessment 4). Following the BPH medications, the number of nocturnal voids in patients with nCPAP plus medication reached nearly the same level of the patients with nCPAP but without BPH medication at Assessment 3 (0.8 ± 0.8 times). Thus, nocturia improved after administration of BPH medication (Figure 1.).

A high percentage of the current subjects, 75%, also had moderate to severe BPH. Masumori et al.[23] analyzed the results of routine examinations of the general population and found that the average volume of the prostate in a typical Japanese man in his 60s and 70s is about 21 or 22 ml. In Japan, a prostate volume of 20 ml or more is considered abnormal.[23),24] In the current study, the volume of the prostate was rather large at 29.7 ± 16.2 ml. Indeed, 30 out of 50 OSA patients (60%) receiving nCPAP treatment also had BPH requiring treatment. Thus, factors related to OSA and BPH were involved in causing nocturia in OSA males over 50. However, the severity of OSA did not directly correlate with prostate volume and the number of nocturnal voids. In patients with OSA, sympathetic activation is elevated in association with faster heart rates, decreased heart rate variability and increased blood pressure variability.[25] This might indirectly worsen BPH and cause increased prostate volume through obstructing the bladder outlet or urethra by contraction of smooth muscle.

Nocturia is also known to be caused by conditions like diabetes and urinary tract infections.[20] In the current study, 8 patients also had type 2 diabetes, but treatment was not administered to any of the patients, there were no complications, and HbA1c was controlled to under 6.5%. In addition, all patients underwent urinalysis, and urinary tract infections like cystitis were ruled out. Thus, we assumed that nocturia due to type 2 diabetes and cystitis was excluded in the current subjects.

This study has several limitations. First, the sample size was small. A further prospective large-scale study is needed. Second, the observation period prior to being seen by urologists was not uniform from 2 to 12 months. However, it would be unethical not to consult urologists for a long time in some patients suffering from severe voids.

In conclusion, BPH is prevalent in patients with moderate to severe OSA. We found that nCPAP alone may be insufficient to treat nocturia for some of patients with OSA. Combining nCPAP treatment and medication for BPH might be considered for the treatment of nocturia

in patients with OSA over the age of 50, when nCPAP is insufficient in treating their nocturia.

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